INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO:
SECTION 25705(b) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

DIISONONYL PHTHALATE (DINP)

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS OF REGULATION

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for diisononyl phthalate (DINP) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 146 micrograms per day (µg/day) is based on carcinogenicity studies conducted in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a voters' initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) is the lead entity responsible for the implementation of Proposition 65.[3] OEHHA has the authority to adopt and amend regulations to further the purposes of the Act.[4] The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are insignificant. The NSRL safe harbor provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

DINP was listed as known to the State to cause cancer under Proposition 65 on December 20, 2013.

---

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as "Proposition 65" or "The Act".
[2] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[3] Title 27, Cal. Code of Regs., section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for DINP, OEHHA relied on a 2013 OEHHA document entitled, "Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP),"[5] which summarizes the available data from rodent carcinogenicity studies of DINP, as well as other information relevant to the carcinogenic activity of the chemical. The NSRL is based upon the results of the most sensitive scientific studies deemed to be of sufficient quality.[6]

Selection of Studies Used to Determine Cancer Potency

OEHHA determined that four two-year diet studies conducted in male and female Fischer 344 (F344) rats and reported by Moore (1998, as reviewed by CPSC, 2001)[7] and Lington *et al.* (1997)[8] met the criterion per Section 25703.

Moore (1998, as reviewed in CPSC, 2001) conducted two long-term carcinogenesis studies of DINP, one in male rats and one in female rats. DINP was administered in the diet to groups of male and female F344 rats at concentrations of 0, 500, 1500, 6000, and 12,000 ppm for 104 weeks. The average daily intake based on food consumption was 29.2, 88.3, 358.7, and 733.2 mg/kg/day for males and 36.4, 108.6, 442.2, and 885.4 mg/kg/day for females. Statistically significant DINP treatment-related increases in combined hepatocellular adenoma and carcinoma and statistically significant increases in leukemia were observed in both sexes. Increases in rare kidney transitional cell carcinoma and uncommon kidney renal tubule cell carcinoma were also observed in male rats, though neither the incidences nor the dose-response trends were statistically significant at the p < 0.05 level. The tumor incidence data used to estimate cancer potency from each of these studies are presented below in Table 1.

---

[5] Office of Environmental Health Hazard Assessment (OEHHA), 2013. Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP). California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, October, 2013, available at:
http://www.oehha.ca.gov/Prop65/hazard_ident/pdf_zip/DINP_HID100413.pdf
[6] Section 25703(a)
[7] Moore MR (1998). Oncogenicity study in rats with di(isononyl)phthalate including ancillary hepatocellular proliferation and biochemical analysis. Covance laboratories, Inc., Vienna, VA. Study No. 2598-104, as reviewed by CPSC (2001). Consumer Product Safety Commission. Report to the US Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on diisononyl phthalate (DINP).
[8] Lington AW, Bird MG, Plutnick RT, Stubblefield WA, Scala RA (1997). Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats. *Funda Appl Toxicol* 36:79-89.

Table 1. Tumor incidences[a] of treatment-related lesions in Fischer 344 rats administered DINP in the diet for two years (Moore 1998, as reviewed by CPSC, 2001)

Organ	Tumor	DINP dietary concentrations (ppm)					Trend test p-value[b]
		0	500	1500	6000	12000	
Male rats							
Liver	Hepatocellular adenoma or carcinoma[c]	5/65	4/50	2/50	7/65	17/65***	$p < 0.001$
Spleen	Mononuclear cell leukemia[d]	22/65	23/55	21/55	32/65*	30/65*	$p < 0.01$
Female rats							
Liver	Hepatocellular adenoma or carcinoma[c]	1/65	1/50	0/50	2/65	8/65*	$p < 0.001$
Spleen	Mononuclear cell leukemia[d]	17/65	16/49	9/50	29/65*	30/65*	$p < 0.001$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined, as reported in OEHHA (2013)

[b] p-values for exact trend test conducted by OEHHA

[c] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, *** $p < 0.001$

[d] p-values associated with mononuclear cell leukemia are based on life table analysis, in which tumors in animals that die prior to terminal sacrifice are regarded as being (directly or indirectly) the cause of death (CPSC, 2001).

Lington *et al.* (1997) conducted two long-term carcinogenesis studies of DINP, one in male rats and one in female rats. DINP was administered in the diet to groups of male and female F344 rats at concentrations of 0, 300, 3000, or 6000 ppm for up to 24 months. The mean daily intakes based on body weight and food consumption were 0, 15, 152, and 307 mg/kg/day for males and 0, 18, 184, and 375 mg/kg/day for females. Statistically significant DINP treatment-related increases in liver carcinoma were observed in male rats and statistically significant increases in leukemia were observed in both sexes. Increases in rare kidney transitional cell carcinoma and uncommon kidney renal tubule cell carcinoma were also observed in male rats, though neither the incidences nor the dose-response trends were statistically significant at the p < 0.05 level. The tumor incidence data used to estimate cancer potency from these studies are presented below in Table 2.

Table 2. Tumor incidences[a] of treatment-related lesions in Fischer 344 rats administered DINP in the diet for two years (Lington et al., 1997)

Organ	Tumor type	DINP dietary concentrations (ppm)				Trend test p-value[b]
		0	300	3000	6000	
Male rats						
Liver	Hepatocellular carcinoma	0/81	0/81	0/80	3/80	$p < 0.015$
Hematopoietic	Mononuclear cell leukemia	33/81	28/80	48/80*	51/80**	$p < 0.001$
Female rats						
Hematopoietic	Mononuclear cell leukemia	22/81	20/81	30/80	43/80***	$p < 0.001$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals examined, as reported in OEHHA (2013)
[b] p-values for exact trend test conducted by OEHHA
Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
NS = not significant

Estimation of Cancer Potency in Rats Using the Linearized Multistage Model

As stated in the 2013 OEHHA document,[9] "The mechanisms by which DINP induces tumors are not known; however, several studies provide information on a number of possible mechanisms of action." Data relevant to several possible mechanisms of DINP carcinogenicity are summarized and discussed in the 2013 OEHHA document.[10]

Based on consideration of all the information summarized in the 2013 OEHHA document, the default approach using a linearized multistage model[11] is applied to derive a cancer potency estimate for each of the four studies. There are not principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of dying with a tumor (p) induced by an average daily dose (d) is given by the multistage polynomial model:

---

[9] Office of Environmental Health Hazard Assessment (OEHHA), 2013. Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP). California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, October, 2013, available at:
http://www.oehha.ca.gov/Prop65/hazard_ident/pdf_zip/DINP_HID100413.pdf
[10] *Ibid.*
[11] Section 25703

$$p(d) = \beta_0 + (1 - \beta_0)\exp[-(\beta_1 \cdot d + \beta_2 \cdot d^2 + ... + \beta_j \cdot d^j)]$$

with constraints $\beta_i \geq 0$ for all i. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor and the parameter β_1 is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received.

The multistage polynomial model defines the probability of dying with a tumor at a single site. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, U.S. EPA's Benchmark Dose Software (BMDS)[12] can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models from the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. In order to derive a measure of the total cancer response to DINP (per mg/kg/day) in a given study, the dose associated with a 5% increased risk of developing a tumor at one or more of the sites of interest was calculated and the lower bound for this dose was estimated using the multisite model in BMDS. The ratio of the extra risk to the lower bound on dose, known as the multisite animal cancer slope factor (CSF$_{animal}$), provides the basis for the animal cancer potency. Animal cancer potencies were estimated for each of the four DINP F344 rat studies described above.

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), the dose in units of mg per kg bodyweight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the four studies described above, scaling to the estimated human potency (CSF$_{human}$) is achieved by multiplying the (multisite) animal potency (CSF$_{animal}$) by the ratio of human to animal body weights (bw$_h$/bw$_a$) raised to the one-fourth power when CSF$_{animal}$ is expressed in units (mg/kg-day)$^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human}/bw_{animal})^{1/4}$$

---

[12] U.S. EPA (Environmental Protection Agency), 2014. Benchmark Dose Software (BMDS) Version 2.5.0.82 [Build: 5/17/2014]. National Center for Environmental Assessment. Available from: http://www.epa.gov/NCEA/bmds/index.html

The default human body weight is 70 kg. The average body weights for the rats were calculated from information presented by Lington *et al.* (1997) and Moore (1998)[13] for control animals during the studies. These values and the derivation of the individual CSF_{human} values using the animal cancer potencies are summarized below in Table 3.

Table 3. Derivation of CSF$_{human}$ and average body weights of control animals in the Lington *et al.* (1997) and Moore (1998) studies

Sex/species	Study	Tumor sites used in estimating potency	Body weight (kg)	CSF$_{animal}$ (mg/kg-d)$^{-1}$	CSF$_{human}$ (mg/kg-d)$^{-1}$
Male rats	Lington 1997	Liver, Leukemia	0.375	0.00284	0.01
	Moore 1998	Liver, Leukemia	0.335	0.000703	0.0027
Female rats	Lington 1997	Leukemia	0.231	0.00165	0.0069
	Moore 1998	Leukemia	0.206	0.000663	0.0028

The geometric mean of the human cancer potency estimates derived from each of the four studies was taken as the basis of the overall cancer potency estimate, yielding a mean potency of 0.0048 (mg/kg-d)$^{-1}$.

Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no significant risk value is one excess case of cancer per one hundred thousand people exposed, expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram bodyweight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the bodyweight for humans. When the calculation is for the general population, the bodyweight is assumed to be 70 kg in NSRL calculations (Section 25703(a)(8)). The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$NSRL = \frac{10^{-5} \times 70\,kg}{CSF_{human}} \times 1000\,\mu g/mg.$$

---

[13] Moore MR (1998). Oncogenicity study in rats with di(isononyl)phthalate including ancillary hepatocellular proliferation and biochemical analysis. Covance laboratories, Inc., Vienna, VA. Study No. 2598-104

As indicated previously, the human cancer slope factor for DINP derived from the data and exposure parameters above is 0.0048 per mg/kg/day. Inserting this number into the equation above results in an NSRL of 146 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline and strikeout.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
Diisononyl phthalate (DINP)	146
…	

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, that does not require a warning or for which a discharge is not prohibited.

NECESSITY

This proposed regulatory amendment would adopt an NSRL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about DINP. The NSRL provides assurance to the regulated community that exposures or discharges at or below them are considered not to pose a significant risk of cancer. Exposures at or below the NSRL are exempt from the warning and discharge requirements of Proposition 65.[14]

---

[14] Health and Safety Code sections 25249.9(b) and 25249.10(c)

BENEFITS OF THE PROPOSED REGULATION

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing a NSRL and therefore may be exposed to litigation for a failure to warn or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing an NSRL, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The 2013 OEHHA document entitled "Evidence on the Carcinogenicity of Diisononyl phthalate (DINP)"[15] is the document relied on by OEHHA for calculating the NSRL for DINP. It includes data used in the potency calculation and on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. A copy of the 2013 OEHHA document will be included in the regulatory record for this proposed action, and is available from OEHHA upon request.

OEHHA relied on the attached Economic Impact Assessment in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt a NSRL for the chemical. Failure to adopt a NSRL would leave the business community without a "safe harbor" level to assist them in determining compliance with Proposition 65.

---

[15] OEHHA, 2011 Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP). California Environmental Protection Agency,

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL provides a "safe harbor" level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

It is not possible to quantify any monetary values for this proposed regulation given that its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation, Elimination, or Expansion of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. DINP is listed under Proposition 65; therefore, effective December 20, 2014 businesses and individuals who manufacture, distribute or sell products with DINP in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Benefits of the Proposed Regulation: The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be exposed to litigation for a failure to warn of an exposure to or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

Problem being addressed by this proposed rulemaking: Proposition 65 does not provide specific guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure that does not require a warning or trigger the discharge prohibition.

How the proposed regulation addresses the problem: The proposed regulation would adopt an NSRL for a listed chemical to provide compliance assistance for businesses that are subject to the requirements of the Act. While OEHHA is not required to adopt such levels, adopting them provides a "safe harbor" for businesses and provides certainty that they are complying with the law if the exposures or discharges they cause are below the established level.

Reasonable alternatives to the proposed regulation: OEHHA determined that the only alternative to the proposed regulation would be to not adopt a NSRL for this chemical. This alternative was rejected because it would fail to provide businesses with the certainty that the NSRL can provide.